J. Physiol. (1955) 127, 143–152

HYPOTHALAMIC CONTROL OF FOOD INTAKE IN CATS AND MONKEYS

By B. K. ANAND, S. DUA and KATE SHOENBERG

From the Department of Physiology, Lady Hardinge Medical College, New Delhi, India

(*Received* 10 *August* 1954)

The role of the central nervous system in regulating food intake was probably suggested first by the discovery that either obesity or emaciation may occur in patients with nervous diseases. For a while these observations were not properly evaluated, because emphasis was laid upon the obesity as such, or the leanness, rather than upon the changed eating habits responsible for the clinical picture. Interest was focused on the hypothalamic region by the experimental studies of many workers (Hetherington, 1941; Hetherington & Ranson, 1940, 1942*a*, *b*; Brobeck, Tepperman & Long, 1943; Kennedy, 1950; Ranson, Fisher & Ingram, 1938) who showed that bilateral lesions in the medial hypothalamus, especially lesions in or ventro-lateral to the ventro-medial nucleus, resulted in obesity. The confusion introduced by the notion that pituitary disturbances caused obesity was also clarified by Hetherington (1943), who showed that the hypophysis is in no way directly concerned with the pathogenesis of obesity following injury to the base of brain. Brobeck *et al.* (1943) demonstrated that this hypothalamic obesity was due to increased food intake (hypothalamic hyperphagia) rather than to disturbances in the fat, carbohydrate or intermediary metabolism. From the time of its discovery this hyperphagia was assumed to be a release phenomenon brought about through the destruction of an inhibitory mechanism.

The existence of another mechanism in the lateral hypothalamus of the rat, which controls the 'instinct' or the 'urge' to eat, was demonstrated by Anand & Brobeck (1951*a*, *b*). They showed that bilateral destruction of a well localized area in the lateral hypothalamus, at the same rostro-caudal level as the ventro-medial nucleus, produces complete aphagia and death due to starvation, in spite of the availability of food. It was also observed that of the two mechanisms the lateral one exerts the more basic type of control over food intake and the medial one (inhibitory) produces its effects only when the lateral

is intact. The lateral mechanism is designated a 'feeding centre', or even an 'appetite centre', while the medial one is called a 'satiety centre'. Joliffe named the two, together, the 'appestat'.

The present study was undertaken to determine, whether similar mechanisms exist in the hypothalamic regions of higher mammals, cats and monkeys, and also whether they are modified by the more highly evolved higher nervous centres.

METHODS

Bilateral electrolytic lesions were produced in the different areas of the hypothalamus of sixteen cats and seventeen monkeys (*macacus*), with the aid of the Horsley-Clarke stereotaxic instrument. Only those animals which recovered consciousness after operation and became awake and active are being reported here. Those that remained somnolent are reported elsewhere. The cats weighed between 2·5 and 4 kg, and the monkeys between 3·5 and 4·5 kg. Intraperitoneal pentobarbitone sodium (M. & B.) was used for anaesthesia (0·7–0·8 ml. of a 5% solution/kg body weight in monkey and 0·8–1 ml. in cat). Intraperitoneal Dial (Ciba) was tried for anaesthesia at first but was discarded as the animals did not recover consciousness for 2–3 days. With pentobarbitone, they recovered consciousness within a few hours after the operation. With the head in the stereotaxic instrument, a small craniotomy was performed, and lesions were produced with a unipolar electrode directed into the hypothalamus. An indifferent electrode applied on the surface of the animal served as an earth. At each point in the hypothalamus, electrolysis was produced by passing a direct current of 3 mA for 30 sec. Lesions of any size can be produced by electrolysis at adjacent points, separated from each other by 1½–2 mm. The co-ordinates of the stereotaxic instrument for different regions of the hypothalamus both in cats and monkeys had been worked out previously.

These animals were fed *ad lib.*, both before and after the production of hypothalamic lesions. A daily record was kept of food intake and weight. The cats were fed on minced meat and milk, and the monkeys on nuts, fresh fruit and vegetables. The animals that developed aphagia were kept alive by feeding on milk and egg mixture by stomach pump, with no tube feeding on certain days to see if the aphagia persisted.

Finally the animals were sacrificed and histological sections made of the brain. These were examined to locate the exact site of the lesions.

RESULTS

Cats

Bilateral hypothalamic lesions were produced in sixteen cats. The following post-operative feeding responses were obtained.

(i) *Aphagia*

In four cats (nos. 7, 11, 15 and 18) eating was completely and permanently abolished in spite of the availability of food in the cage. All these recovered consciousness within a few hours of the operation and, except for aphagia, did not seem to be abnormal. They were awake and active, did not show any neurological deficits, and their rectal temperatures were normal. They refused food not only when it was placed in contact with their lips and teeth, but even when it was placed inside their mouths. They were kept alive by stomach tube feeding for periods ranging from 1 to 4 weeks. During these periods tube feeding

was withheld periodically for as long as 2 days without the cats showing any spontaneous desire to eat. The feeding response of one of them is shown in Fig. 1. In this (no. 11) the tube feeding was stopped and it died from starvation, without eating the available food.

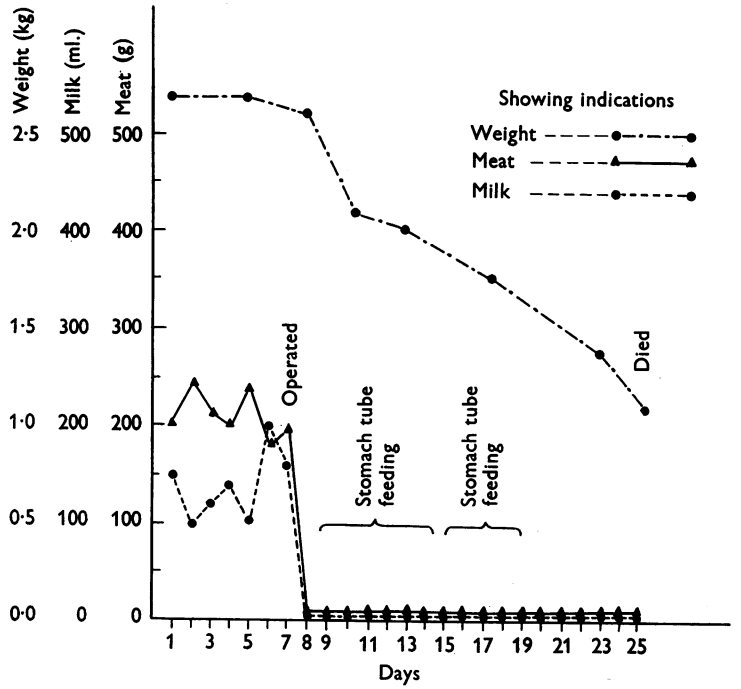

Fig. 1. Food intake (spontaneous) and weight chart of cat 11 which developed complete aphagia after hypothalamic lesions.

All histological sections of the aphagic animals showed bilateral destruction of the same region, i.e. the lateral-most region of the lateral hypothalamus in the plane of the central part of the middle hypothalamus (median eminence region) (Figs. 2*a* and 3*a*). In one animal (no. 11), in addition to this area, the lesions had also progressed rostrally into the anterior hypothalamus (Fig. 2*b*), while in two (nos. 15 and 18) the lesions had also progressed caudally into the posterior hypothalamus (Fig. 3*b*). Other adjacent structures (medial hypothalamus, fornix, internal capsule, optic tract, etc.) were mostly left intact.

(ii) *Hyperphagia*

Two cats (nos. 2 and 10) developed hyperphagia after the operation. In cat 2 the daily intake of both meat and milk was markedly increased, while cat 10 did not eat for 4–5 days and later developed an increased desire for food. Histological sections showed bilateral destruction of the medial hypothalamic area in the region of the median eminence (Fig. 4), leaving the lateral

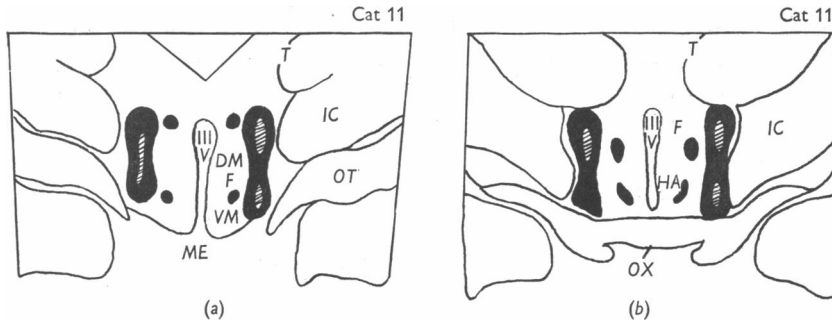

Fig. 2. Drawings of sections through diencephalon of cat 11. Lesions have destroyed the lateral parts of middle (*a*) and anterior hypothalamus going up to suprachiasmal region (*b*), producing aphagia. Lettering for this and later figures: *DM*, nucleus hypothalamicus dorso-medialis; *F*, fornix; *HA*, nucleus hypothalamicus anterior; *HL*, nucleus hypothalamicus lateralis; *HP*, nucleus hypothalamicus posterior; *IC*, internal capsule; *MB*, mammillary body; *ME*, median eminence; *OT*, optic tract; *OX*, optic chiasma; *PV*, nucleus paraventricularis; *T*, thalamus; *VM*, nucleus hypothalamicus ventro-medialis; III *V*, third ventricle.

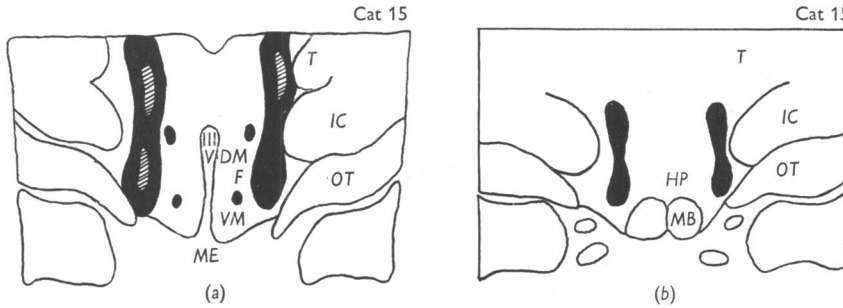

Fig. 3. Sections through diencephalon of cat 15. Lesions have destroyed the lateral parts of middle (*a*) and posterior hypothalamus going up to mammillary region (*b*), producing aphagia.

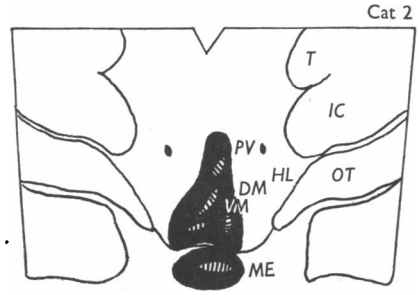

Fig. 4. Lesions destroying the medial hypothalamus in the region of median eminence, producing hyperphagia. Lateral hypothalamus is spared.

hypothalamus intact. In cat 10 bilateral lesions were later produced in the lateral hypothalamic region described above. After this hyperphagia changed to complete aphagia.

(iii) *Normal eating*

The remaining ten cats showed no change in their feeding responses after the operations. Histologically these showed lesions which were either rostral (Fig. 5) or caudal (Fig. 6) to the two hypothalamic regions described above (i and ii), which in every case were left intact.

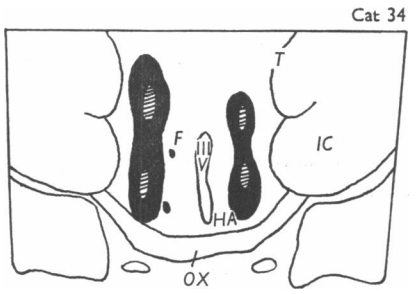

Fig. 5

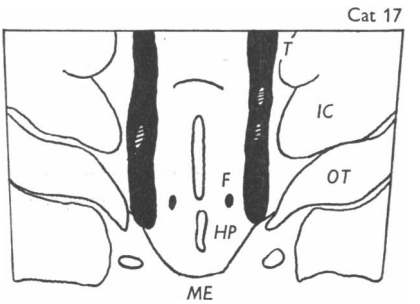

Fig. 6

Fig. 5. Lesions destroying the suprachiasmal (anterior) hypothalamic regions only. No change in food intake.

Fig. 6. Lesions destroying the posterior hypothalamic regions only. No change in food intake.

In some animals, which showed lesions adjacent to the lateral area, food intake was completely stopped or decreased for the first few days, but returned to normal later on.

Monkeys

The seventeen monkeys, with bilateral hypothalamic lesions showed the following post-operative feeding responses.

(i) *Aphagia*

In four monkeys (nos. 2, 11, 12 and 18), the operations were followed by complete cessation of eating and they would not eat even when the food was put into their mouths. Two other monkeys (nos. 4 and 7), on the other hand, would not eat the food easily available to them in the cage, in spite of starvation, but when the food was put directly into their mouths they would bite on it and swallow it. These two could be kept alive by putting the food into their mouths, while the other four had to be fed by stomach tube. They were kept alive for periods ranging from 1 to 4 weeks. All six recovered consciousness within a few hours after the operation, and none of them, except no. 4 (see below), showed any apparent abnormality or neurological deficit. Their rectal temperatures were normal.

Histological examination in all these showed bilateral destruction of the lateral hypothalamus in the plane of the central part of middle hypothalamus (median eminence region) (Figs. 7*a*, 8*a*). Histologically no difference could be

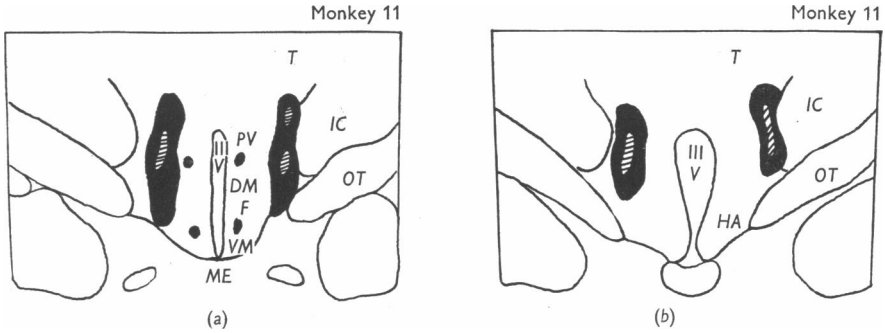

Fig. 7. Sections through diencephalon of monkey 11. Lesions have destroyed the lateral parts of middle (*a*) and anterior hypothalamus (*b*), producing complete aphagia.

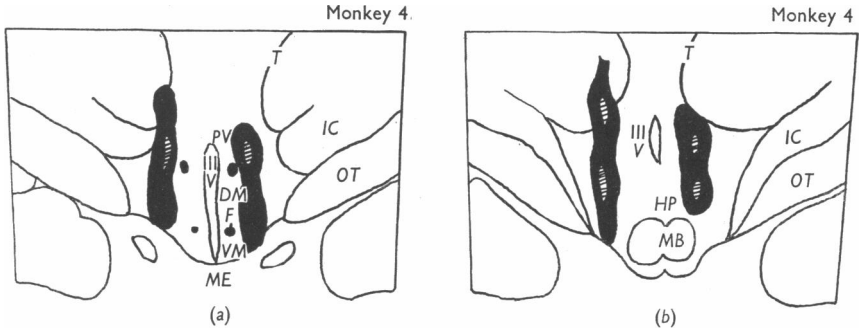

Fig. 8. Lesions destroying the lateral parts of middle (*a*) and posterior hypothalamus going up to mammillary region (*b*). It would not eat food available in the cage, but would swallow food put into its mouth.

demonstrated between the lesions in monkeys 4 and 7 and monkeys 2, 11, 12 and 18. In one animal (no. 11) the lesions had progressed rostrally into the anterior hypothalamus (Fig. 7*b*), in two (nos. 4 and 7) they had progressed into the posterior hypothalamus (Fig. 8*b*), while in the other three they were localized to the lateral part of the middle hypothalamus. Monkey 4 showed generalized tremors involving the head and limbs, and histological study revealed that the lesion on the left side had damaged the caudate nucleus in addition to the hypothalamic region.

(ii) *Hyperphagia*

One monkey (no. 3) developed hyperphagia after the operation. Histological sections showed involvement of the medial hypothalamus in the region

of the median eminence. Later on bilateral lesions were placed in the lateral hypothalamus of this animal and this changed the feeding response into complete aphagia.

(iii) *Normal eating*

The remaining ten monkeys did not show any change in their feeding behaviour as a result of the hypothalamic lesions. In eight of these, the lesions were shown to be either rostral or caudal to the two hypothalamic regions described above (i and ii), which were spared. In monkey 13, although the lesions were in the same plane as described above (i), the lesion on one side was in the lateral hypothalamus, while on the other side it was well outside the

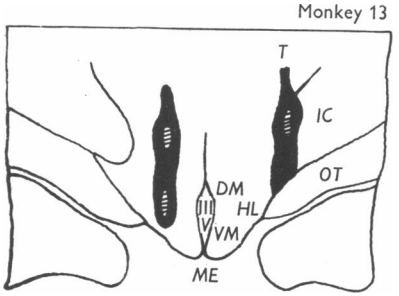

Fig. 9

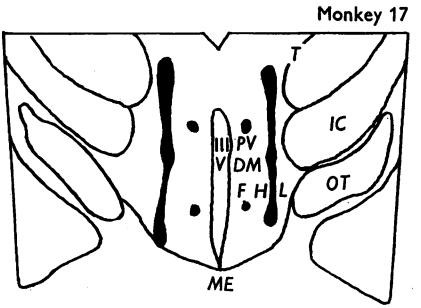

Fig. 10

Fig. 9. Asymmetrical lesions destroying the lateral parts of middle hypothalamus on the right side, but outside the hypothalamus on the left side. No change in food intake.

Fig. 10. Little destruction of the lateral parts of middle hypothalamus. No change in food intake.

lateral hypothalamus. Thus only unilateral destruction of the lateral hypothalamus had been produced (Fig. 9). In monkey 17, although the tracks of the electrode were seen in the region of the lateral hypothalamus described above (i), somehow no electrolysis had been produced (Fig. 10).

None of the cats or monkeys with hypothalamic lesions showed any rage reaction (Wheatley, 1944; Bard & Mountcastle, 1948).

DISCUSSION

The present study appears to confirm the existence of the same hypothalamic mechanisms controlling the feeding response in cats and monkeys as were previously demonstrated in the rat (Anand & Brobeck, 1951*a*, *b*).

Development of hyperphagia by bilateral destruction of the region in the neighbourhood of the ventro-medial nucleus has been shown by various workers in the rat. On the other hand, hyperphagia in cats has been demonstrated only by Wheatley (1944) and Anand & Brobeck (1951*b*), and in monkeys by

Ranson *et al.* (1938) and Ruch, Patton & Brobeck (1942). The first three groups of workers obtained hyperphagia after producing bilateral lesions involving the region of the ventro-medial nucleus only, while Ruch *et al.* obtained it from more caudally placed lesions of the ventral part of the thalamus and the rostral portion of the mesencephalic tegmentum. In the present study all the hyperphagic animals had lesions in the region of the ventro-medial nucleus and none of the animals with caudal lesions gave this response. As reported previously (Anand & Brobeck, 1951*a*, *b*), even in these higher mammals, the hyperphagia could be obtained only if the lateral hypothalamus (feeding centre) was left intact. After bilateral destruction of the lateral hypothalamus in these hyperphagic animals (cat 10 and monkey 3), the hyperphagia changed into complete aphagia.

In an earlier report, Anand & Brobeck (1951*a*, *b*) reported the existence of areas in the lateral hypothalamus of the rat, at the same rostro-caudal plane as the ventro-medial nucleus, which when bilaterally destroyed lead to complete inhibition of food intake. The present study confirms the existence of similar areas in cats and monkeys. Destruction of these areas bilaterally leads to aphagia. Unilateral destruction of this area does not produce aphagia (monkey 13) and this is in conformity with the observations that unilateral injury to the medial hypothalamus does not lead to hyperphagia, and that stimulation of either side of the hypothalamus usually affects both sides of the visceral nervous system, and probably of the somatic as well. Failure of spontaneous eating for variable periods following hypothalamic injury has also been reported incidentally in cats by Clark, Magoun & Ranson (1939), Ingram, Barris & Ranson (1936), and Anand & Brobeck (1951*b*), and in monkeys by Ranson (1939). Delgado & Anand (1953), on the other hand, showed increased food intake in some cats by stimulation of this lateral hypothalamic region.

Thus the hypothalamus of the higher mammals, monkey and cat, possesses both the mechanisms controlling feeding behaviour, the more lateral area being designated a 'feeding centre' and the more medial a 'satiety centre'. According to Brobeck (personal communication), these hypothalamic mechanisms probably do not represent the most basic mechanisms of feeding behaviour, which must be reflex in nature, as the hypothalamus is too high in the brain stem to represent a really fundamental neural circuit. The feeding reflexes may be initiated by the sight, odour, or sound of food, or contact with it. The hypothalamic centres have probably the function of facilitation (lateral hypothalamus), and inhibition (medial hypothalamus) of these reflexes. Hunger contractions may also be included as a source of central facilitation. It is not yet quite clear what activates the inhibitory mechanism (satiety centre) and brings about satiation of the animal. Strominger & Brobeck (1953) think it is the specific dynamic action of the food ingested.

Although all the cats (in common with the rats previously reported) with bilateral lesions in the 'feeding centre' developed complete and permanent aphagia, out of the six monkeys having lesions in this area, only four had complete aphagia, while the other two would not eat the food by themselves, but would take it when the food was put directly into their mouths (monkeys 4 and 7). This may be explained on the basis of the monkey possessing phylogenetically a higher type of neocortex than the cat and rat, and may be advanced as a further proof, if one is needed, for more functions being taken over by the neocortex from the basal regions. It may not be out of place to mention here that, although both obesity and cachexia are seen in clinical cases with damage to the hypothalamic region, both hyperphagia and anorexia are also often reported as post-operative reactions to lobotomy, in which no damage has been done to the hypothalamic region.

The neural mechanism regulating feeding, therefore, appears to be based upon feeding reflexes, which are selectively facilitated or inhibited by higher centres. These have definitely been located in the hypothalamic region, and also may be present higher up. Confirmatory evidence in support of this concept of the hypothalamic centres being the facilitatory and inhibitory mechanisms for the feeding reflexes has been obtained by studying the feeding responses, as well as by some biochemical studies, in cats after stimulation of different hypothalamic regions by means of implanted electrodes. These results are being presented elsewhere (Anand & Dua, 1955).

SUMMARY

1. Bilateral electrolytic lesions were produced in different hypothalamic regions in sixteen cats and seventeen monkeys to study the results of these lesions on the feeding responses.

2. Bilateral destruction of the lateral hypothalamus in the plane of the central part of the median eminence (same rostro-caudal plane as the ventromedial nucleus) produced aphagia.

3. Bilateral destruction of the medial hypothalamus in the region of the ventro-medial nucleus produced hyperphagia, provided the lateral hypothalamus was intact. If the lateral hypothalamus is also destroyed, there is aphagia, in spite of the medial lesions.

4. Lesions in other hypothalamic regions do not change the feeding response.

5. The localization of a 'feeding centre' in the lateral hypothalamus and a 'satiety centre' in the medial hypothalamus, previously reported in the rat, is therefore established in cat and monkey.

6. Two monkeys, made aphagic by bilateral destruction of the 'feeding centre' would eat if the food was directly placed in their mouths. This difference may be due to a plylogenetically more highly evolved neocortex in monkeys as compared with cats and rats.

7. The neural mechanism regulating feeding appears to be based upon feeding reflexes which are selectively facilitated or inhibited by higher centres.

The authors thank Dr C. L. Birch for her help and guidance in writing this paper.

This work was aided by a grant-in-aid from the Indian Council of Medical Research. Research equipment was supplied by the Rockefeller Foundation of New York.

REFERENCES

ANAND, B. K. & BROBECK, J. R. (1951*a*). Localisation of a 'feeding centre' in the hypothalamus of the rat. *Proc. Soc. exp. Biol. N.Y.*, **77**, 323–324.

ANAND, B. K. & BROBECK, J. R. (1951*b*). Hypothalamic control of food intake in rats and cats. *Yale J. Biol. Med.* **24**, 123–140.

ANAND, B. K. & DUA, S. (1955). *Indian J. med. Res.* (In the Press.)

BARD, P. & MOUNTCASTLE, V. B. (1948). Some forebrain mechanisms involved in expression of rage with special reference to suppression of angry behaviour. *Res. Publ. Ass. nerv. ment. Dis.* **27**, 362–404.

BROBECK, J. R., TEPPERMAN, J. & LONG, C. N. H. (1943). Experimental hypothalamic hyperphagia in the albino rat. *Yale J. Biol. Med.* **15**, 831–853.

CLARK, G., MAGOUN, H. W. & RANSON, S. W. (1939). Hypothalamic regulation of body temperature. *J. Neurophysiol.* **2**, 61–80.

DELGADO, J. M. R. & ANAND, B. K. (1953). Increase of food intake induced by electrical stimulation of the lateral hypothalamus. *Amer. J. Physiol.* **172**, 162–168.

HETHERINGTON, A. W. (1941). The relation of various hypothalamic lesions to adiposity and other phenomena in the rat. *Amer. J. Physiol.* **133**, 326–327.

HETHERINGTON, A. W. (1943). The production of hypothalamic obesity in rats already displaying chronic hypopituitarism. *Amer. J. Physiol.* **140**, 89–92.

HETHERINGTON, A. W. & RANSON, S. W. (1940). Hypothalamic lesions and adiposity in the rat. *Anat. Rec.* **78**, 149–172.

HETHERINGTON, A. W. & RANSON, S. W. (1942*a*). The relation of various hypothalamic lesions to adiposity in the rat. *J. comp. Neurol.* **76**, 475–499.

HETHERINGTON, A. W. & RANSON, S. W. (1942*b*). The spontaneous activity and food intake of rats with hypothalamic lesions. *Amer. J. Physiol.* **136**, 609–617.

INGRAM, W. R., BARRIS, R. W. & RANSON, S. W. (1936). Catalepsy—an experimental study. *Arch. Neurol. Psychiat., Chicago*, **35**, 1175–1197.

KENNEDY, G. C. (1950). The hypothalamic control of food intake in rats. *Proc. Roy. Soc.* B, **137**, 535–549.

RANSON, S. W. (1939). Somnolence caused by hypothalamic lesions in the monkey. *Arch. Neurol. Psychiat., Chicago*, **41**, 1–23.

RANSON, S. W., FISHER, C. & INGRAM, W. R. (1938). Adiposity and diabetes mellitus in a monkey with hypothalamic lesions. *Endocrinology*, **23**, 175–181.

RUCH, T. C., PATTON, H. D. & BROBECK, J. R. (1942). Hyperphagia and adiposity in relation to disturbances of taste. *Fed. Proc.* **1**, 76.

STROMINGER, L. & BROBECK, J. R. (1953). A mechanism of regulation of food intake. *Yale J. Biol. Med.* **25**, 383.

WHEATLEY, M. D. (1944). The hypothalamus and affective behaviour in cats. *Arch. Neurol. Psychiat., Chicago*, **52**, 296–316.